A Heterodinuclear Asymmetric Catalyst for Conjugate Additions of α-Hydroxyketones to β-Substituted Nitroalkenes
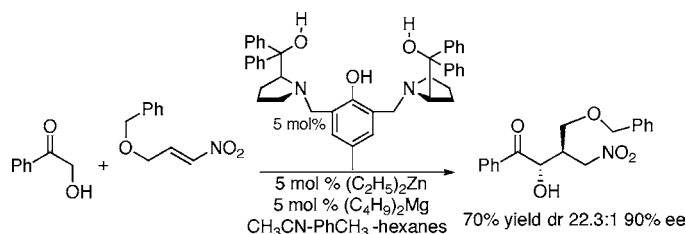
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ABSTRACT

The bis-ProPhenol ligand was designed to facilitate formation of hetereodinuclear complexes based upon the large difference in pK_a of the one phenolic OH group to the tertiary OH groups. In exploring the first example of hydroxyacetophenones as donors in asymmetric Michael reactions with nitroalkene acceptors, the best stereocontrol was observed with a zinc/magnesium dinuclear complex where enantiomeric excesses ranged up to 92% for the major anti diastereomer.

The development of heterodinuclear complexes for catalysis remains a scantily developed area.[1] Particularly noteworthy is the work of Shibasaki using heteropolynuclear complexes for asymmetric catalysis.[2] Our design of the bis-ProPhenol ligands[3] (eq 1) was meant to enable formation of heterodinuclear complexes by virtue of the large difference in pK_a between the phenolic and tertiary alcohol hydroxy groups. We began our studies of the prospect of forming heterobimetallic complexes for asymmetric catalysis in the context of asymmetric conjugate additions,[4] particularly of nitroalkenes because of the synthetic versatility of the nitro group and of the versatility of the adducts.[5,6] The juxtaposition of functionality created by the use of α-hydroxyacetophenones as donors focused our efforts on them since they have not previously been reported with this class of Michael acceptors to the best of our knowledge.[7] Herein, we report the first

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(6) Hydroxyacetone as a donor has frequently given poor selectivities or requires large excesses and long reaction times. See: (a) Andrey, O.; Alexakis, A.; Bernardinelli, G. *Org. Lett.* **2003**, *5*, 2559. (b) Betancourt, J.M.; Sakthrivel, K.; Thayumanavan, R.; Tanaka, F.; Barbas, C.F. III *Synthesis* **2004**, 1509. (c) Mitchell, C. E. T.; Cobb, A. J. A.; Ley, S. V. *Synlett* **2005**, 611. (d) Xu, Y.; Cordova, A. *Chem. Commun.* **2006**, 460. (e) Wang, J; Li, H.; Low, B.; Zu, L.; Guo, H.; Wang, W. *Chem.—Eur. J.* **2006**, *12*, 4321.

example wherein a heterodinuclear complex from **1** functions as an asymmetric catalyst.

a) M$_1$ = M$_2$ = Zn
b) M$_1$ = Zn M$_2$ = Mg
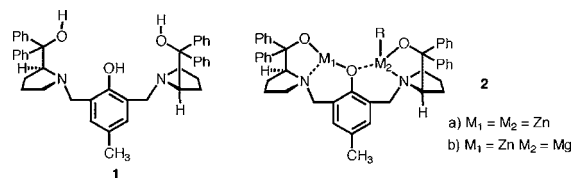
In a test reaction, 1.1 equiv of phenylnitroalkene and 1.0 equiv of α-hydroxyacetophenone (0.6 M in ketone) were mixed with 5 mol % of the standard Zn−Zn catalyst (**2a**) in the stated solvent at +5 °C (eq 1).
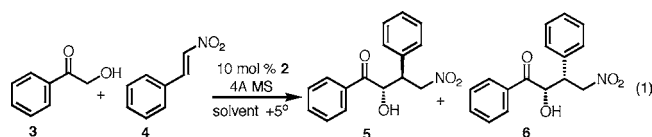
As summarized in Table 1, entries 1−4, in virtually every solvent, the anti products showed high enantiomeric excesses (ee's), whereas the syn products were formed with poor ee's. The best ee's were observed in the least Lewis basic solvents. Unfortunately, the diastereoselectivities were poor.

Table 1. Optimization of the Selectivities

entry	R$_n$M[a]	solvent[b]	time (h)	yield (%)[c]	anti:syn	% ee anti[d]
1	(C$_2$H$_5$)$_2$Zn/(C$_2$H$_5$)$_2$Zn	PhCH$_3$	44	89	1.3:1.0	99[e]
2	(C$_2$H$_5$)$_2$Zn/(C$_2$H$_5$)$_2$Zn	CH$_2$Cl$_2$	44	64	1.1:1.0	99
3	(C$_2$H$_5$)$_2$Zn/(C$_2$H$_5$)$_2$Zn	THF	44	77	1.0:1.0	89
4	(C^{2}H$_5$)$_2$Zn/(C$_2$H$_5$)$_2$Zn	DME	44	98	1.0:1.4	90
5	(C$_4$H$_9$)$_2$Mg/(C$_4$H$_9$)$_2$Mg	THF	18	91	1.6:1.0	32[f]
6	(C$_2$H$_5$)$_2$Zn/(C$_4$H$_9$)$_2$Mg	THF	28	89	2.1:1.0	90[g]
7	(C$_2$H$_5$)$_2$Zn/(C$_4$H$_9$)$_2$Mg	PhCH$_3$	42	63	1.4:1.0	82
8	(C$_2$H$_5$)$_2$Zn/(C$_4$H$_9$)$_2$Mg	CH$_2$Cl$_2$	32	71	2.3:1.0	91
9	(C$_2$H$_5$)$_2$Zn/(C$_4$H$_9$)$_2$Mg	DME	21	93	2.5:1.0	91
10	(C$_2$H$_5$)$_2$Zn/(C$_4$H$_9$)$_2$Mg	CH$_3$CN	14	96	2.4:1.0	89[h]
11	(C$_2$H$_5$)$_2$Zn/(CH$_3$)$_3$Al	THF	18	83	1.0:1.0	81
12	(CH$_3$)$_3$Al/(C$_4$H$_9$)$_2$Mg	THF	18	72		4

[a] In each case, 2 equiv of total organometallic reagent per ligand was employed. [b] (C$_2$H$_5$)$_2$Zn is 1.1 M in PhCH$_3$; (C$_4$H$_9$)$_2$Mg is 1.0 M in heptanes. [c] Total of the isolated yields for pure anti and syn. The diastereomers were isolated by column chromatography with the fast eluting diastereomer being the syn isomer and the slow eluting isomer anti. [d] The ee's were determined by chiral HPLC on a Chiracel OD column. [e] The syn isomer had an ee of 18%. [f] The syn isomer had an ee of 9%. [g] The syn isomer had an ee of 23%. [h] The syn isomer had an ee of 25%.

While we also examined some variation of the ligand with no appreciable differences in the result, we considered an alternative strategy involving change of metal. Use of

(7) In a different catalyst system, requirements for an ortho methoxy group in the hydroxyacetophenone have been reported for Michael additions to other acceptors for good enantioselectivities. See: (a) Matsunaga, S.; Kimoshita, T.; Okada, S.; Harada, S.; Shibasaki, M. *J. Am. Chem. Soc.* **2004**, *126*, 7559. (b) Harada, S. Kumagai, N.; Kinoshita, T.; Matsunaga, S.; Shibasaki, M. *J. Am. Chem. Soc.* **2003**, *125*, 2582.

magnesium rather than zinc gave a faster reaction with somewhat better diastereomeric ratio (dr) but poorer ee (entry 5). The ligand design which consists of one phenolic OH and two tertiary alcohols should allow installation of two different metals because of the dramatic difference in pK_a of these two types of OH. Since magnesium gave better dr's than zinc and zinc gave better ee's, we examined a mixed metal Zn/Mg system (entries 6−10) wherein we add 1 equiv each of diethylzinc and di-*n*-butylmagnesium per ligand sequentially. The best results to date were indeed obtained with this mixed system in a more polar toluene/hexanes/acetonitrile solvent wherein the anti isomer was isolated in 67% yield and the dr determined by isolation of each pure diastereomer.

Adopting entry 10 as the "standard" set of conditions, because it was fastest and gave the best yield and selectivities with a 5 mol % catalyst loading, we varied the donor by using five-membered ring heterocycles (eq 2).

a) X = O
b) X = S

yield 91%, dr 3.3:1, *anti* 99% ee
yield 72%, dr 2.7:1, *anti* 77% ee
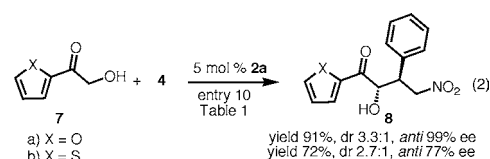
While the furan **7a** gave excellent results, there was a diminishment in the ee with the thiophene derivative **7b**, which may derive from the thiophilicity of zinc. The anti isomers of **8a** and **8b** can be isolated in 70 and 53% yields, respectively, and the dr's can be determined by isolation. Thus, both five- and six-membered ring aromatic donors are good partners.

Table 2 summarizes the variation of the nitroalkene (eq 3) using the standard conditions with 5 mol % of catalyst to give the adducts **9**. In virtually every case, the dr's are higher than those of the 2-nitrostyrene case. Five-membered ring heterocycles as well as ortho-substituted six-membered aryl rings give good selectivities. Interestingly, even a conjugated alkyne gave only the simple conjugate adduct with good selectivity (entry 7).
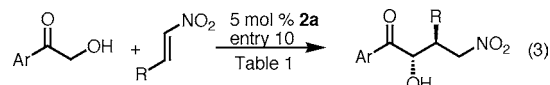
The relative stereochemistry being anti as drawn was established by X-ray crystallography of the product **9c**. The absolute stereochemistry was established as shown in eq 4 by direct reduction to the amino diol **10** followed by oxidative cleavage.
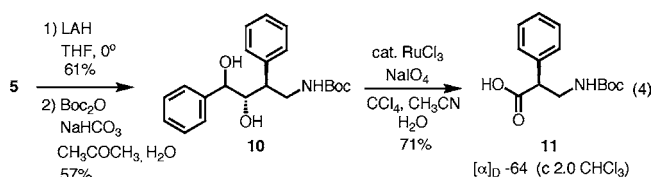

This known 2-substituted β-amino acid[8] **11** had a rotation

Table 2. Variation of the Acceptor[a]

entry	Ar	R	product	yield[b] %	anti:syn[c]	% ee anti
1	Ph	(furyl)	**9a**	69 (58)	5.3:1.0	90
2	Ph	(thienyl)	**9b**	86 (72)	5.1:1.0	89
3	Ph	(o-OCH₃-phenyl)	**9c**	59 (46)	3.6:1.0	92
4	Ph	BnO~CH₂	**9d**	70 (67)	22.3:1.0	90
5	(furyl)	(benzodioxole)	**9e**	97 (67)	2.2:1.0	76
6	(furyl)	H₃CO–C₆H₄	**9f**	59 (46)	3.6:1.0	91
7	(furyl)	(t-Bu alkyne)	**9g**	80 (67)	5.2:1.0	87
8	(furyl)	TIPS–alkyne	**9h**	41	>99:1	90
9	(furyl)	BnO~CH₂	**9i**	56 (50)	8.3:1.0	91
10	(furyl)	(dioxolane)	**9j**	80 (67)	5.2:1.0	89

[a] All reactions were performed with 1.0 equiv of hydroxyketone and 1.1 equiv of nitroolefin in acetonitrile at +5 °C with 5 mol % of catalyst prepared from 5 mol % of ligand **1**, 5 mol % of $(C_2H_5)_2Zn$, and 5 mol % of $(C_4H_9)_2Mg$. [b] Sum of isolated yields with isolated yield of major diastereomer given in parentheses. [c] Determined by isolation of anti and syn isomers.

corresponding to the *S*-enantiomer as depicted. Thus, this also serves as an asymmetric route to such β-amino acids.[9] These adducts also serve as a convenient intermediate for the asymmetric synthesis of pyrrolidines, such as **12** as illustrated in eq 5.

$$\mathbf{5} \xrightarrow[\substack{C_2H_5OH, CH_2Cl_2 \\ 91\%}]{\substack{H_2 \ (1 \ atm) \\ Pd/C}} \mathbf{12} \qquad (5)$$
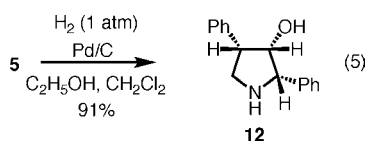
The stereochemistry is assigned as all cis based upon the observed NOE effects of the three methine hydrogens (Figure 1).
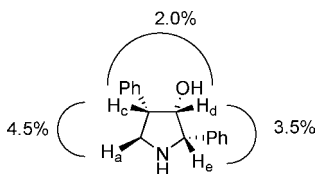
Figure 1. NOE data for pyrrolidine **12**.

Scheme 1 proposes a catalytic cycle based upon the X-ray structure of the homodinuclear zinc complex[10] that accounts

Scheme 1. Proposed Catalytic Cycle
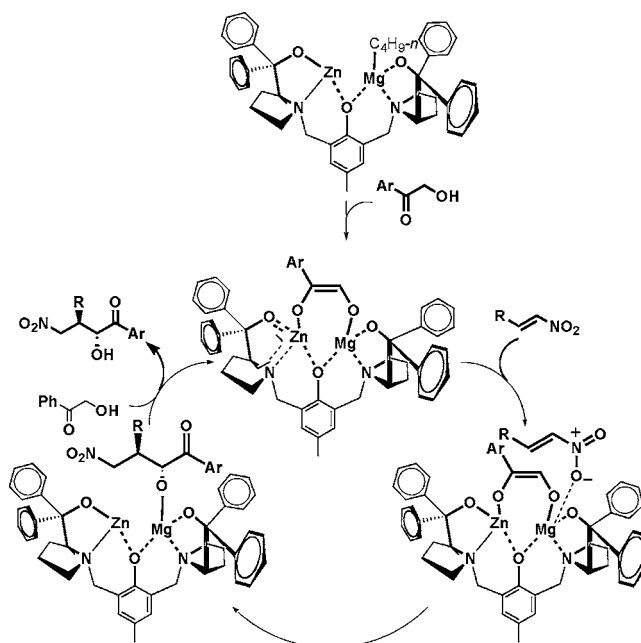
for the observed selectivity. This represents the first example of a heterodinuclear complex with this ligand in an asymmetric catalytic reaction. The reactions reported herein only need equimolar ratios of reactants and reaction times of 18–42 h to generate a highly differentially functionalized adduct that permits selective manipulation of the functionalities. The utility of the juxtaposition of the functionality is demonstrated by the one-step asymmetric synthesis of pyrrolidines. The benefit demonstrated herein of using two different metals with the chiral scaffold **1** stimulates the broad exploration of various metals that may expand the scope of asymmetric catalytic processes possible.

Supporting Information Available: Experimental procedures and characterization data for all new compounds (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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